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200mM hypertonic saline resuscitation attenuates intestinal injury and inhibits p38 signaling in rats after severe burn trauma

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ABSTRACT

Background: An overabundant discharge of inflammatory mediators plays a significant role in intestinal injury throughout the early stages of critical burns. The present study aims to explore the outcome of 200mM hypertonic saline (HS) resuscitation on the intestinal injury of critically burned rats.

Materials and methods: Fifty-six Sprague-Dawley rats were randomized into three groups: sham group (group A), burn plus lactated Ringer's group (group B), and burn plus 200mM HS group (group C). Samples from the intestine were isolated and assayed for wet-weight-to-dry-weight (W/D) ratio, histopathology analyses, and p38 mitogen-activated protein kinase (MAPK) activity. Serum interleukin 1β (IL-1β) and high mobility group protein box 1 (HMGB1) concentrations were also examined.

Results: Initial resuscitation with 200mM Na^+ HS significantly decreased the intestinal W/D ratio and improved intestinal histopathology caused by severe burn. HS resuscitation also inhibited the increase of serum IL-1β and HMGB1 concentrations, and p38 MAPK activity in the intestine of critically burned rats.

Conclusions: The overall findings of this study suggest that preliminary resuscitation with 200mM HS after severe thermal injury reduces intestinal edema, inhibits systemic inflammatory response, and attenuates intestinal p38 MAPK activation, thus reduces burns-induced intestinal injury.

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1. Introduction

The gut plays a major beneficial role by providing vital functions in regards to the endocrine and immune systems, as well as its important role as a defensive barrier against bacteria, fungi, and other organisms. There are two major roles of intestinal epithelial cells, the first being nutrient and liquid absorption and the second being a barrier in order to eliminate injurious antigens and to decrease the possibility of infiltration of microorganisms [1,2]. Disturbance of the intestinal epithelial barrier has been verified after burn trauma, which can promote the intestinal bacteria and their products (*e.g.*, endotoxin) translocation to the blood circulation, by this means initiating or propagating an inflammatory response in critically burned individuals [1,3,4]. Intestinal injury has been suggested to be the driving force of the systemic inflammatory response syndrome, acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome (MODS) [5–7].

The Parkland-Baxter formula is the most frequently used resuscitation parameter to guide initial fluid administration for severely burned patients [8]. However, this formula sometimes results in over-resuscitation in burn victims [9]. "Fluid creep" was a term to describe a phenomenon that burn patients receiving far more fluid [9]. Fluid creep has been documented to be correlated with the complications of ALI/ARDS and/or abdominal compartment syndrome (ACS) [10]. ACS in critical burns has been linked to a mortality rate of 70–100% [11–13].

To reduce over-resuscitation, a group of scientists used hypertonic crystalloids separately or in conjunction with colloids [14–16]. When administered *in vivo*, hypertonic resuscitation fluids display significant anti-inflammatory properties that cause a reduction in secondary organ damage in numerous animal models of trauma, hemorrhagic shock, and sepsis [17–21]. Many studies have revealed that hypertonic saline (HS) had beneficial effects in shock resuscitation by decreasing general edema and abdomen impediments in severely burned patients [22–24]. Nevertheless, Huang et al. described series of patient deaths associated with hypernatremia succeeding HS administration and there was an intensification in renal dysfunction with HS [24]. The heavy sodium concentration of resuscitation fluid (240-300 mM of Na^+) was regarded as the cause of high morbidity. A slight hypertonic crystalloid mixture of lactated Ringer's fluid plus 50 mM sodium bicarbonate (180 mM of Na^+) was proposed to reduce the complication of HS [25].

A disproportionate release of cytokines, such as interleukin (IL)-1β, high mobility group protein box 1 (HMGB1), and oxidative stress was associated with the amplified vascular permeability and systemic edema throughout the early period after critical burns [26–32]. Our previous study has shown that the preliminary resuscitation with 200 mM HS after critical burn trauma reduces pulmonary edema, prevents hyponatremia, and decreases oxidative damage [33]. In this study, we investigated the effect of 200 mM hypertonic crystalloid resuscitation on burn-induced intestinal injury by examining the inflammatory mediators such as IL-1β, HMGB1, and signal transduction pathway in critically burned rats to determine the probability and mechanism of slight HS resuscitation after thermal injury.

2. Materials and methods

2.1. Animals

Sprague-Dawley rats (healthy, adult, 200–250 g weight body, provided by Anhui Medical University in Hefei, China) were used throughout the study. All experimental operations were commenced in accordance with the authorization of the animal experimental ethics committee of Anhui Medical University in Hefei city, China. Rats were permitted one week to familiarize to their environment. Animals were nurtured using a typical animal diet; food and water were accessible at will during the course of the study procedure.

2.2. Burn procedure

Tail vein catheters were situated in all rats under general analgesia and anesthesia by pentobarbital injecting intraperitoneally (30 mg/kg); the dorsal surfaces were then de-haired by shaving them and the rats were safeguarded in an assembled template device. The superficial area of the dorsal surface, which was left unprotected through the template device, was submerged in water at a temperature of 98 °C for 12 s. The rats were all dried directly after being burned by hot water to circumvent further injury. This procedure, allowed for a full-thickness dermal burn comprising of 30% total body surface area (TBSA) to be achieved.

2.3. Experimental design

Fifty-six Sprague-Dawley rats were randomized into three groups: sham group (group A, n=8), burn plus lactated Ringer's group (group B, n=24), and burn plus 200 mM HS group (group C, n=24). Group A: rats were immersed in room-temperature water and did not receive any fluid resuscitation. Group B, animals were resuscitated with intravenous sodium lactate Ringer's injection according to the Parkland formula [11], with 12.5% that amount administered in the first 2 h and 50% in the first 8 h after a 30% full-thickness burn. Group C, burned rats were resuscitated with 200 mM HS in the same matter. In the group C, the initial fluid of the first 24 h was based on the volume of hypertonic fluid calculated to deliver the same sodium load as estimated by Parkland formula (sodium 0.52 mEq/kg body weight/% BSA burn). The constitution of one liter of the HS resuscitation fluid was comprised of 955.41 mL sodium lactate Ringer's solution with 44.59 mL 10% NaCl (1700 mM). The HS fluid consisted of Na^+ 200 mM, Cl^- 180 mM, K^+ 3.8 mM, Ca^{++} 2.9 mM, and lactate 27 mM. The rats of group B and C were sacrificed at 2, 8, and 24 h after burn trauma in order to sample their blood and tissue.

2.4. Preparation of small intestinal tissues

Four small intestinal sections were harvested at a distance of 10 cm distal to the ligament of Treitz by laparotomy; then were carefully washed using 4 °C saline. Two small intestinal

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